Voriconazole: the newest triazole antifungal agent

NICKIE D. GREER, PHARMD

Fungal infections remain a significant cause of morbidity and mortality despite advances in medicine and the emergence of new antifungal agents (1). Immunocompromised patients are particularly at risk of developing these infections, with *Candida* and *Aspergillus* spp. being the mycoses most commonly identified (2). Patients who develop candidemia have a greater chance of prolonged hospitalization and have a mortality rate as high as 60%. In addition, the prevalence of *Candida* spp. that are resistant to triazole antifungal agents is increasing, making treatment options a concern. Aspergillosis carries a 100% mortality rate if left untreated (3). Although there are numerous treatment options, no broad-spectrum antifungal agents with an acceptable safety profile and with both intravenous and oral formulations are available at this time.

Amphotericin B is currently the drug of choice for the treatment of systemic infections caused by *Aspergillus* and *Candida* spp. (2–4). However, the high incidence of toxicity associated with amphotericin B has limited its use in many patients. Lipid formulations of amphotericin B are better tolerated than conventional amphotericin B and have similar efficacy. However, these agents are costly and are generally reserved for second-line therapy in patients who did not respond to or could not tolerate conventional amphotericin B therapy. Caspofungin, an echinocandin antifungal agent, has in vitro activity against *Aspergillus* and *Candida* spp. However, due to a lack of clinical trials, it is generally reserved for aspergillosis that is refractory to other antifungal treatment. Fluconazole and itraconazole are triazole antifungal agents used in the treatment of fungal infections. They have both intravenous and oral formulations and favorable safety profiles. However, the triazoles' spectrum of activity is somewhat limited. Fluconazole is active mainly against *Candida albicans* and *Cryptococcus neoformans*. Itraconazole is most active against *Aspergillus* spp. and has greater activity than fluconazole against resistant strains of *Candida* spp. other than *C. albicans* (2).

Voriconazole is the newest agent in the armamentarium against fungal infections. It is a triazole antifungal with a structure related to that of fluconazole and a spectrum of activity comparable to that of itraconazole. Voriconazole was approved by the Food and Drug Administration in May 2002 for the treatment of invasive aspergillosis and refractory infections of *Scedosporium apiospermum* and *Fusarium* spp. Studies have also shown it to be a promising agent for empiric treatment in febrile neutropenia.

INDICATIONS

Voriconazole (VFEND, Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland) is a triazole antifungal agent that inhibits fungal ergosterol biosynthesis (5). It is structurally related to fluconazole, with the major difference being the substitution of a fluoropyrimidine grouping in place of a triazole moiety (5, 6). Voriconazole is indicated for the treatment of invasive aspergillosis. It is also indicated for the treatment of fungal infections caused by *S. apiospermum* or *Fusarium* spp. that are refractory to other antifungal agents (5).

PHARMACOLOGY

Like the other triazole antifungals, voriconazole exerts its antifungal activity by inhibition of 14-alpha-lanosterol demethylation, which is mediated by fungal cytochrome P450 enzymes (2, 5, 6). This inhibition is more selective for fungal than for mammalian enzyme systems. The accumulation of 14-alpha-methyl sterols results in a decrease in ergosterol, which is an essential component of fungal cell wall formation. The resulting cell wall abnormalities are thought to be responsible for voriconazole's antifungal activity.

PHARMACOKINETICS

The pharmacokinetic profile of voriconazole has been defined from various studies in healthy volunteers, patients, and special populations (5, 7–9). Voriconazole is unique because of its saturable metabolism, resulting in a nonlinear Michaelis-Menten pharmacokinetic profile. Thus, when the dosage of voriconazole is increased, a larger-than-proportional increase is seen in drug exposure. This also results in a variable elimination half-life (from 6 to 24 hours) depending on the dosage of voriconazole given.

The pharmacokinetic properties of voriconazole are similar whether given intravenously or orally. It is well absorbed, with an oral bioavailability of >95%. It takes 1 to 2 hours to reach maximum concentrations after dosing. However, the bioavailability is decreased and the time to maximum concentration extended when voriconazole is administered with a high-fat

From the Department of Pharmacy Services, Baylor University Medical Center, Dallas, Texas.

Corresponding author: Nickie D. Greer, PharmD, Department of Pharmacy Services, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, Texas 75246 (e-mail: NickiG@BaylorHealth.edu).

meal (2, 5). Absorption is not diminished when voriconazole is administered with gastric acid–suppressing agents such as cimetidine, ranitidine, or omeprazole.

Voriconazole is extensively distributed into tissue, with a volume of distribution of approximately 4.6 L/kg (5). A case study reports that cerebrospinal concentrations were 42% to 67% of plasma concentrations in 2 patients with acute leukemia who had *Aspergillus* spp. meningitis (10). Protein binding is approximately 58% in plasma and is independent of various plasma drug concentrations reached after single and multiple oral doses.

Voriconazole is extensively metabolized in the liver to the N-oxide metabolite (5, 8, 10). The main hepatic cytochrome P450 enzyme responsible for voriconazole's metabolism is CYP2C19, although CYP2C9 and CYP3A4 are also involved. Studies performed in vitro suggest that voriconazole, as well as its metabolite, inhibits these enzymes as well. CYP2C19 is subject to genetic polymorphism, leaving certain populations susceptible to decreased metabolism and increased plasma levels of voriconazole. Persons of Asian descent have up to a 20% chance of being a poor metabolizer, while Caucasian and African American individuals have up to a 5% chance (11). Studies have indicated that poor metabolizers can have an area under the curve up to 4 times higher than that of homozygous extensive metabolizers and 2 times higher than that of heterozygous extensive metabolizers. Poor metabolizers also have higher plasma accumulation after multiple dosing.

SPECTRUM OF ACTIVITY

Voriconazole has shown activity against *Aspergillus* spp. in vitro (8, 12–16). Growth-inhibition studies have shown voriconazole to be fungicidal against the various *Aspergillus* spp. Voriconazole and itraconazole have similar minimum inhibitory concentrations (MICs) when tested against *Aspergillus* spp. Voriconazole demonstrated low MICs for all *Aspergillus* spp. tested but appeared to be most active against *Aspergillus fumigatus*. Abraham and colleagues also found that voriconazole maintains activity against itraconazole-resistant *A. fumigatus* isolates (17). This suggests that voriconazole may have alternate mechanisms of fungal killing since complete cross-resistance did not develop.

Voriconazole has also shown activity against *Candida* spp. (8, 14, 16–18). Growth-inhibition studies demonstrated that voriconazole, like itraconazole, is fungistatic against all *Candida* spp. tested. Voriconazole and itraconazole had the lowest MICs for *C. albicans* isolates but had MICs up to 32 times higher for other *Candida* strains. Overall, voriconazole showed more potency than fluconazole or itraconazole for most *Candida* isolates studied. Although potency is maintained against fluconazole-resistant *Candida* spp., the MICs are higher than in those that are fluconazole sensitive, suggesting the possibility of cross-resistance with voriconazole and other azoles.

Voriconazole has been studied in other mycoses as well (2, 5, 8, 14–16, 19–21). It has shown in vitro efficacy against *S. apiospermum*, *S. prolificans*, *C. neoformans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Pseudallescheria boydii*. Voriconazole had greater activity against *S. apiospermum* than miconazole, posaconazole, or itraconazole (MIC 0.5 μg/mL, 1 μg/mL, 2 μg/mL, and 4 μg/mL, respectively). Voriconazole was also found to have a lower MIC than itraconazole or fluconazole against *C. neoformans* (0.125–0.25 μg/mL, 16 μg/mL, and 0.5 μg/mL, respectively). Further trials are needed to determine the role of voriconazole in infections caused by these fungi.

CLINICAL EFFICACY

Treatment of invasive aspergillosis

Denning and colleagues conducted an open, noncomparative, multicenter trial to evaluate the efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis (22). Patients were included in the study if they were older than 14 years and had probable or definite invasive aspergillosis. Patients were permitted to receive salvage treatment with voriconazole if they had previously received amphotericin B, liposomal amphotericin B, or itraconazole at therapeutic doses. Patients who had received other antifungal agents or lower-than-treatment doses were considered to be receiving primary therapy when voriconazole was initiated. Therapy was initiated with two 6-mg/kg intravenous loading doses 12 hours apart and was continued with 3 mg/kg intravenously at 12-hour intervals for 6 to 27 days. Patients were then switched to oral therapy (200 mg twice daily) for 4 to 24 weeks. Complete response was defined as complete resolution of all clinical signs and symptoms as well as complete radiographic resolution. Partial response was defined as major improvement or resolution of clinical signs and symptoms and improvement in radiographic findings by at least 50%. Failure was defined as progression of infection or death due to invasive aspergillosis. "Good response" was defined as either complete or partial response.

In total, 116 patients were assessable for efficacy and 137 for safety. Of the assessable patients, 14% had a complete response, 34% a partial response, and 21% a stable response to voriconazole therapy. Thirty-one percent of patients did not respond to therapy. Good response was seen in 60% of patients with pulmonary or tracheobronchial disease, 16% of patients with cerebral disease, and 50% of patients with disseminated disease. Good response was also seen in 58% of patients with underlying hematologic disorders and 26% of patients who had undergone allogeneic stem cell transplant. Patients receiving voriconazole as primary therapy had a good response rate of 59%, while those receiving salvage therapy had a good response rate of 38% ($P = 0.02$). Thirty-eight percent of patients with a definite diagnosis of aspergillosis had a good response, whereas the good response rate was 58% in those with probable disease ($P = 0.05$). Patients who died during therapy and had autopsy results confirming disease were classified as definite cases.

The most common adverse events were visual disturbances, abnormal liver function test results, and rash. Fifteen of the 137 patients developed visual disturbances, described as blurry vision or as seeing wavy lines. This generally occurred shortly after dosing and resolved after a few minutes, with no permanent visual problems reported. Twenty patients developed abnormal liver function test results requiring discontinuation of drug therapy. The majority of these patients had plasma voriconazole concentrations >6000 ng/mL. The authors concluded that voriconazole is safe and efficacious for the primary treatment of invasive aspergillosis.

Herbrecht and colleagues conducted a randomized, nonblinded trial to compare voriconazole with amphotericin B for

the treatment of invasive aspergillosis in immunocompromised patients (23). Patients were randomized to receive either voriconazole or amphotericin B for a total of 12 weeks. Patients randomized to the voriconazole group received two 6-mg/kg doses intravenously on day 1 and then 4 mg/kg intravenously twice daily for at least 7 days, followed by 200 mg orally twice daily. Patients randomized to the amphotericin B group received a dose of 1 to 1.5 mg/kg intravenously once daily. If response to initial therapy was inadequate, the patients could be switched to other antifungal agents. A data review committee that was blinded to treatment allocation assessed the certainty of diagnosis and response to therapy at week 12 and at the end of initial randomized therapy. The modified intention-to-treat population included 277 patients who received at least 1 dose of the assigned study medication and who had a diagnosis of definite or probable invasive aspergillosis. The primary efficacy endpoint was demonstration of the noninferiority of voriconazole compared with amphotericin B at week 12 in the modified intention-to-treat population. Secondary endpoints included the demonstration of voriconazole superiority compared with amphotericin B at the end of initial therapy, survival rates at week 12, and safety.

Baseline characteristics were similar between groups, with the only significant difference being that the voriconazole group included a higher number of patients with definite aspergillosis (46.5% vs 30.8%, $P = 0.01$). The median duration of voriconazole treatment was 77 days, of which 10 days were intravenous therapy. The median duration of amphotericin B treatment was 10 days (mean dose 0.97 mg/kg). Other antifungal therapy was initiated in 52 patients in the voriconazole group and 107 patients in the amphotericin B group, with lipid formulations of amphotericin B being the most common substitution. A successful outcome (complete or partial response) was noted in 52.8% of patients in the voriconazole group and 31.6% of patients in the amphotericin B group (95% confidence interval [CI] 10.4% to 32.9%). This degree of success was consistent regardless of site of infection, neutropenic status, or underlying disease state. In the intention-to-treat population, the success rate was 49.7% in the voriconazole group and 27.8% in the amphotericin B group (95% CI 12.4% to 31.2%). At week 12, the survival rate was 70.8% in the voriconazole group and 57.9% in the amphotericin B group ($P = 0.02$).

Significantly fewer adverse events occurred in the voriconazole group than in the amphotericin B group ($P = 0.02$). Visual disturbances were the most common side effects in the voriconazole group, while chills, fever, and renal impairment were the most common side effects in the amphotericin B group. The authors concluded that voriconazole has superior response rates, survival rates, and safety in patients with invasive aspergillosis compared with amphotericin B. However, it is important to note that since the median treatment time with amphotericin B was 10 days, 107 of 133 patients (80%) in the amphotericin B group were changed to alternate therapy. These alternate therapies included lipid formulations of amphotericin B (n = 47), itraconazole (n = 38), and unspecified antifungals or combinations of drugs (n = 22). Thus, voriconazole was essentially compared with other antifungal therapy as well as with amphotericin B.

Empiric antifungal therapy in neutropenia

Walsh and colleagues conducted a randomized, multicenter, open-label trial comparing voriconazole with liposomal amphotericin B (L-AMB) for empiric antifungal therapy in neutropenic patients with persistent fever (24). Patients were stratified at enrollment according to the risk of fungal infection. High-risk patients were those who had received allogeneic hematopoietic stem cell transplants or were receiving chemotherapy for relapsed leukemia. Other patients were classified as being at moderate risk of fungal infections. Patients randomized to the voriconazole group received a 6-mg/kg loading dose every 12 hours for 2 doses and then a maintenance dose of 3 mg/kg intravenously every 12 hours. Patients could be switched to oral voriconazole (200 mg every 12 hours) after at least 3 days of intravenous therapy. L-AMB was given at a dose of 3 mg/kg intravenously per day. If there was evidence of a fungal infection, the voriconazole dose was increased to 4 mg/kg intravenously every 12 hours (or 300 mg orally every 12 hours) and L-AMB was increased to 6 mg/kg per day. Additionally, if toxic effects occurred, the dose of L-AMB could be decreased to 1.5 mg/kg per day. No dosage adjustments were allowed for voriconazole unless there had been a prior dose escalation. Treatment was continued for up to 3 days after neutrophil recovery (absolute neutrophil count >250 cells/mm^3) or up to a maximum of 12 weeks in those with documented fungal infections. The primary endpoint was successful treatment, defined as no breakthrough fungal infections, survival 7 days past the end of therapy, no premature discontinuation of study medication, fever resolution during the period of neutropenia, and successful treatment of baseline fungal infection. The secondary endpoints were safety and tolerability of each therapy.

In total, 415 patients in the voriconazole group and 422 patients in the L-AMB group were included in the modified intention-to-treat group, and all baseline characteristics were similar. Voriconazole and L-AMB had similar success rates (26% vs 30.6%, respectively; 95% CI –10.6% to 1.6%). This confidence interval fell outside the predefined lower limit of –10 percentage points required to show noninferiority. Breakthrough fungal infections were documented in 8 patients in the voriconazole group and in 21 patients in the L-AMB group ($P = 0.02$). Of these 29 patients, 48.3% died from invasive mycosis, while the overall mortality rate in this study was 12.9%. Those patients at high risk for fungal infection had fewer breakthrough fungal infections with voriconazole (1.4%) than with L-AMB (9.2%; $P = 0.003$). The complete or partial response rate of patients who had baseline fungal infections was 46.2% in the voriconazole group and 66.7% in the L-AMB group (95% CI –67.0% to 25.9%). The overall mortality rate of the 2 groups did not differ significantly. Voriconazole was discontinued more often than L-AMB because of lack of efficacy (22 vs 5; $P = 0.001$); persistent fever was the most common cause for discontinuation. None of these fevers was due to a documented fungal infection. Patients at moderate risk had a lower success rate with voriconazole (23%) than with L-AMB (31%; 95% CI –15.2% to –0.4%), although the authors attributed this to the disparity in mortality from progressive cancer between the groups. Patients receiving voriconazole experienced more visual disturbances and visual hallucinations than patients receiving L-AMB. Patients receiving L-AMB experienced more azotemia and hypokalemia than

patients in the voriconazole group. There was no significant difference in the incidence of hepatotoxicity between the groups, although this may not be applicable to patients undergoing longer treatment for proven fungal infections.

The authors concluded that voriconazole is appropriate for empirical antifungal therapy in neutropenic patients and may be used in lieu of L-AMB. However, it is important to note that the difference in success rates was greater than the limit of the study's definition of noninferiority, meaning that it cannot be inferred that the 2 agents are equivalent. It is not clear whether this reflects a problem in study design or an actual difference in efficacy between the 2 drugs. *P* values were not reported for any outcome data in the study (although these are reported in the annotated package insert). Moreover, the authors presented the unstratified analysis in their report rather than the stratified analysis that was planned prospectively before the study began (25). Subgroup analysis showed that patients at high risk of fungal infection had better outcomes with voriconazole, but this study was not powered to detect definite differences in subgroup analyses. The finding that the voriconazole-treated patients had fewer breakthrough fungal infections while on treatment is also suspect, as the total number of breakthrough infections was low and the study was not powered to detect a difference in the number of these infections. Furthermore, voriconazole may have been discontinued more often than L-AMB because the study was nonblinded and clinicians were cautious about continuing study drug if patients remained febrile. Notably, the rate of successful treatment with L-AMB in this study was lower (30.6%) than that reported in previous studies in febrile neutropenic patients (50%–64%) (26–28). However, this may be due to divergent definitions of fever resolution among the studies. The L-AMB study did not specify a time requirement for fever resolution, while the voriconazole trial required patients to be afebrile during the period of neutropenia or prior to the end of treatment, whichever came first.

Treatment of esophageal candidiasis

Ally and colleagues conducted a randomized, double-blind, double-dummy, multicenter trial comparing the efficacy of voriconazole with that of fluconazole for the treatment of esophageal candidiasis in immunocompromised patients (29). Patients were randomized to receive voriconazole or fluconazole plus placebo for 2 to 6 weeks. Patients in the voriconazole group received 400 mg orally twice daily and placebo. Patients in the fluconazole group received 400 mg orally once and then received 200 mg orally every day plus placebo. Treatment continued for 7 days after the resolution of all clinical signs and symptoms but was not allowed to extend past 42 days of therapy. The primary endpoint was to demonstrate that voriconazole was not inferior to fluconazole for the treatment of esophageal candidiasis. This endpoint was based on response to treatment assessed by esophagoscopy on day 43 or at the end of treatment. This analysis was performed on the per-protocol and intention-to-treat populations, and success was defined as esophagitis cured or improved. The intention-to-treat group included all patients who received at least 1 dose of study medication, and the per-protocol group included patients who had no significant deviations from the inclusion and exclusion criteria. Secondary efficacy endpoints assessed the symptomatic resolution of esophageal and oropharyngeal candidiasis and the time to clinical cure.

There were 191 and 141 patients treated with fluconazole and 200 and 115 patients treated with voriconazole in the intention-to-treat and per-protocol groups, respectively. An endoscopically proven cure was seen in 94.8% of patients in the voriconazole group and in 90.1% of patients in the fluconazole group. The success rate (cured or improved) was 98.3% for patients receiving voriconazole and 95.1% for patients receiving fluconazole (95% CI –1.0% to 75%). This fell within the predefined noninferiority margin of –15 percentage points. Symptoms resolved in 82% of patients treated with voriconazole and 83.2% of patients treated with fluconazole. The success rate (symptoms cured or improved) was 88% for the voriconazole group and 91.1% for the fluconazole group (95% CI –9.2% to 3.0%). The success rates for oropharyngeal candidiasis were 88.4% for patients treated with voriconazole and 93.8% for patients treated with fluconazole (95% CI –12% to 1.0%). At the 4-week follow-up, 5.7% of patients in the voriconazole group and 10.3% of patients in the fluconazole group had a relapse. The median time to cure was similar in both groups (8 days). Treatment-related adverse events were more common in the voriconazole group. Visual disturbances and abnormal liver function test results were more common in the voriconazole group. The authors concluded that voriconazole is at least as effective as fluconazole for the treatment of esophageal candidiasis. Of note, the number of patients needed to achieve power was not disclosed in this study, so it is unknown if enough patients were enrolled to prove noninferiority. Additionally, *P* values were not reported for any parameters.

Treatment of other pathogens

Voriconazole has been studied in the treatment of other fungal pathogens as well. In one pooled analysis, successful response to voriconazole was seen in 15 of 24 patients (63%) with *S. apiospermum* infection (5). In 3 of these patients, the infection relapsed within 4 weeks of follow-up. Nine of 24 patients (43%) with *Fusarium* spp. infection were successfully treated with voriconazole. Two of these patients experienced relapse. However, these studies were pooled analyses, and complete review of the data was not possible.

RESISTANCE

The development and frequency of resistance to voriconazole has not been adequately studied (5, 8). The main mechanisms of resistance to the triazole antifungal agents include ergosterol biosynthesis pathway modification, changes in gene expression, and increased expression of efflux pumps through various genes. Fungal isolates that demonstrate reduced susceptibility to fluconazole or itraconazole may show reduced susceptibility to voriconazole, although the relevance of this finding has not been fully defined. For this reason, if triazole cross-resistance is demonstrated, alternative antifungal therapy is recommended.

ADVERSE EFFECTS/TOXIC EFFECTS

Voriconazole's safety has been evaluated in patients and healthy volunteers throughout phase I and clinical trials (5, 8). It is generally well tolerated, with visual disturbances, fever, rash,

hepatic abnormalities, nausea, vomiting, abdominal pain, and headache being the most commonly reported adverse effects. The adverse events most often responsible for discontinuation of therapy include visual disturbances, elevated hepatic function test results, and dermatologic reactions.

Approximately 30% of patients in clinical trials experienced visual disturbances, including altered or enhanced visual perception, blurred vision, color vision change, and/or photophobia (5, 8). Patients receiving higher doses or patients with higher plasma concentrations may be more likely to experience visual abnormalities. These disturbances were generally mild in nature, occurred within 30 minutes of dosing, and lasted approximately 30 minutes. Visual disturbances generally occurred during the first week of therapy and were reversible after the patient discontinued therapy or became tolerant to voriconazole. The retina appears to be the site of action, although the actual mechanism of action for the visual disturbances is unknown. One study evaluated the retinal function of healthy volunteers receiving voriconazole for 28 days (5). The study found that voriconazole caused ocular abnormalities on both the retinal rods and cones. Electroretinogram waveform amplitude and visual field were decreased and alterations in color perception were observed, and these abnormalities continued throughout the treatment period. Patients were tested again 14 days after treatment discontinuation, and the electroretinogram, visual fields, and color perception had returned to baseline in most subjects (2, 5, 8). Long-term vision impairment risk in humans is not known, so the manufacturer recommends that physicians monitor visual function for patients receiving voriconazole for periods longer than 28 days.

Table 1. Effects of voriconazole on the metabolism of other drugs*

Drug	Mechanism of interaction	Result	Recommendation
Astemizole, terfenadine, cisapride, pimozide, quinidine	CYP3A4 inhibition	↑ plasma concentrations QT prolongation	Contraindicated
Sirolimus	CYP3A4 inhibition	↑ plasma concentrations	Contraindicated
Rifabutin	CYP3A4 inhibition	↑ plasma concentrations	Contraindicated
Ergot alkaloids (ergotamine, dihydroergotamine)	CYP450 inhibition	↑ plasma concentrations	Contraindicated
Cyclosporine	CYP3A4 inhibition	↑ AUC and ↑ trough level	Decrease cyclosporine dose by half; monitor levels
Tacrolimus	CYP3A4 inhibition	↑ AUC and C_{max}	Decrease tacrolimus dose by one third; monitor levels
Phenytoin	CYP2C9 inhibition	↑ plasma concentrations	Monitor phenytoin levels
Warfarin	CYP2C9 inhibition	↑ PT/INR	Monitor PT/INR
Omeprazole	CYP2C19/3A4 inhibition	↑ plasma concentrations	Reduce omeprazole dose by half if initial dose >40 mg
Protease inhibitors	CYP3A4 inhibition	↑ plasma concentrations	Monitor for toxicity
Nonnucleoside reverse-transcriptase inhibitors	CYP3A4 inhibition	↑ plasma concentrations	Monitor for toxicity
Benzodiazepines	CYP3A4 inhibition	↑ plasma concentrations	Monitor for toxicity
HMG-CoA reductase inhibitors (statins)	CYP3A4 inhibition	↑ plasma concentrations	Monitor for toxicity
Dihydropyridine calcium channel blockers	CYP3A4 inhibition	↑ plasma concentrations	Monitor for toxicity
Sulfonylureas	CYP2C9 inhibition	↑ plasma concentrations	Monitor blood glucose, signs/symptoms of hypoglycemia
Vinca alkaloids	CYP3A4 inhibition	↑ plasma concentrations	Monitor for toxicity

*Adapted from references 2 and 5.

AUC indicates area under the curve; C_{max}, maximum concentration; HMG-CoA, hydroxymethylglutaryl coenzyme A; INR, international normalized ratio; PT, prothrombin time.

Abnormalities in hepatic transaminase levels occurred in 13.4% of patients in clinical trials (2, 5, 8). Hepatic transaminase and alkaline phosphatase increases >3 times the upper limit of normal were more frequent in patients receiving voriconazole than in patients receiving other antifungal agents in clinical trials. These abnormalities have been associated with higher concentrations or higher doses of voriconazole, but specific parameters have not been established at this time (30). Transaminases generally returned to baseline levels either during treatment (with or without dosage adjustment) or after discontinuation. Voriconazole has been associated with hepatic toxicity, including jaundice, hepatitis, and acute hepatic failure leading to death. It is recommended that hepatic function tests be evaluated at initiation and during the course of voriconazole therapy. If hepatic function test results or bilirubin levels become elevated, patients should be evaluated for progression to more severe hepatic injury. Discontinuation of therapy should be considered for any patient who develops hepatic disease that may be attributed to voriconazole.

Skin reactions attributed to voriconazole occurred in approximately 6% of patients in clinical trials (2, 5, 8). Most reactions were mild to moderate in severity and did not require treatment discontinuation. It is important to note that many patients were receiving steroids, antihistamines, and other immunosuppressants that might affect the severity and the presentation of the skin reaction. Photosensitivity may occur, particularly in patients receiving voriconazole for a long period. There have been rare cases (4) of patients developing serious cutaneous reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme) when receiving voriconazole. Patients who develop a dermatologic reaction should be monitored closely, and voriconazole should be discontinued if the reaction increases in severity.

DRUG INTERACTIONS

Voriconazole affects the metabolism of several other drugs *(Table 1)*, and other drugs affect its metabolism as well *(Table 2)*.

Table 2. Effects of other drugs on the metabolism of voriconazole*

Drug	Mechanism of interaction	Result	Recommendation
Rifampin	Enzyme induction	↓ plasma concentrations	Contraindicated
Rifabutin	Enzyme induction	↓ plasma concentrations	Contraindicated
Carbamazepine	Enzyme induction	↓ plasma concentrations	Contraindicated
Barbiturates	Enzyme induction	↓ plasma concentrations	Contraindicated
Phenytoin	Enzyme induction	↓ plasma concentrations	Increase voriconazole maintenance dose to 5 mg/kg IV or 400 mg PO every 12 hours
Protease inhibitors	CYP3A4 inhibition	↑ plasma concentrations	Monitor for toxicity
Nonnucleoside reverse-transcriptase inhibitors	CYP3A4 inhibition Enzyme induction	↑ plasma concentrations ↓ plasma concentrations	Monitor for toxicity Monitor for effectiveness

*Adapted from references 2 and 5.

DOSE/DOSAGE FORMS

Voriconazole injection is supplied as a sterile lyophilized powder in a single-use vial containing 200 mg of active drug and 3200 mg of sulfobutyl ether beta-cyclodextrin sodium (5). For the treatment of fungal infections in adults, the dose of intravenous voriconazole is 6 mg/kg every 12 hours for 2 doses, followed by a maintenance dose of 4 mg/kg. If patients are unable to tolerate this dosage because of side effects, the dose may be decreased to 3 mg/kg intravenously every 12 hours. In clinical studies, a maintenance dosage of 3 mg/kg intravenously every 12 hours was given when patients received voriconazole empirically for neutropenic fever. Patients who are able to take oral medications may be switched to oral voriconazole.

Oral voriconazole is supplied as film-coated tablets containing 50 mg or 200 mg of active drug. For the treatment of fungal infections in adults, the dose of voriconazole is 400 mg orally every 12 hours for 2 doses, followed by a maintenance dose of 200 mg orally every 12 hours. If patient response is not adequate, a dosage of 300 mg orally every 12 hours may be given. For patients weighing <40 kg, the loading dose and maintenance dose should be halved. If a patient is intolerant to treatment, the oral dose may be decreased in 50-mg increments.

Patients with mild to moderate hepatic insufficiency (Child-Pugh class A and B) should receive standard loading dose regimens of voriconazole. However, the maintenance dosage should be halved based on dosing studies demonstrating that the area under the curve was prolonged in these groups of patients (5, 8). No data are available at this time for the pharmacokinetics of voriconazole in patients with severe hepatic insufficiency.

Patients with mild, moderate, or severe renal dysfunction (including those on dialysis) may receive oral voriconazole at the usual recommended dosages. Dosing studies have demonstrated that the area under the curve of oral voriconazole is not altered at any level of renal dysfunction (5, 8). However, dosing studies also revealed that when intravenous voriconazole was given to patients with renal impairment, accumulation of the solubilizing excipient occurred. This compound has been associated with nephrotoxic effects such as cytoplasmic vacuolation in the renal tubule epithelium, renal pelvis, and urinary bladder. It is for this reason that patients with a creatinine clearance <50 mL/min should not receive intravenous voriconazole unless the benefits for use outweigh the potential risks.

PHARMACOECONOMICS

Table 3 outlines the cost of treatment with antifungals for a 30-day course of therapy. For the treatment of invasive aspergillosis, the drugs voriconazole, caspofungin, itraconazole, liposomal amphotericin B, and amphotericin B were compared at standard dosages. As expected, intravenous therapy is the most expensive route of administration. L-AMB treatment at 5 mg/kg is approximately $14,000 per month of therapy. Voriconazole given intravenously for 30 days is similar in cost to caspofungin and lower-dose L-AMB ($7556, $8266, and $8498, respectively). However, it is approximately $2700 more than intravenous itraconazole for 30 days of treatment, making itraconazole a more attractive choice for *Aspergillus* spp. treatment if intravenous therapy is anticipated for the entirety of treatment. If voriconazole is converted to oral dosing after 7 days of treatment, the cost is reduced to $2520 for 30 days of therapy. This is a difference of approximately $5000 per patient compared with a 30-day course of intravenous voriconazole and is approximately the same cost as an intravenous-to-oral conversion of itraconazole. This would also result in a $6000 to $12,000 savings compared with a 30-day treatment course of L-AMB.

For the treatment of candidiasis, the drugs voriconazole, caspofungin, and fluconazole were analyzed. The dosage of voriconazole used in the comparison was that used in the study done in patients with esophageal candidiasis (29).

The costs of empiric therapy with voriconazole, amphotericin B, or L-AMB were analyzed. The dosage of voriconazole used in the comparison was that used in the study done in patients with febrile neutropenia (24).

SUMMARY

Fungal infections remain a significant cause of morbidity and mortality despite advances in medicine and the emergence of new antifungal agents. Voriconazole is the newest agent in the armamentarium against fungal infections. It is a triazole antifungal with a structure related to that of fluconazole and a spectrum of activity comparable to that of itraconazole. Voriconazole is indicated for the treatment of invasive aspergillosis and for the treatment of fungal infections caused by *S. apiospermum* and *Fusarium* spp. that are refractory to other antifungal agents.

Voriconazole is available in both intravenous and oral formulations; the oral bioavailability reaches approximately 95%. Having both formulations available allows conversion to oral therapy for patient convenience and cost containment. Unlike

Table 3. Cost comparison of 30-day treatment with antifungal agents*

Condition and drug	Dosing regimen	Cost/30-day treatment ($)
Aspergillosis		
Voriconazole IV	6 mg/kg × 2, then 4 mg/kg q12 (70 kg)	7555.73
Voriconazole PO	400 mg × 2, then 200 mg q12	1514.04
Voriconazole PO	200 mg × 2, then 100 mg q12 (<40 kg)	403.22
Voriconazole PO	400 mg × 2, then 300 mg q12 (dose increase if response inadequate)	2222.80
Voriconazole IV to PO	6 mg/kg IV × 2, then 4 mg/kg IV q12 × 7 days, then 200 mg PO q12 × 21 days	2520.18
Caspofungin IV	70 mg × 1, then 50 mg QD	8265.65
Itraconazole IV	200 mg q12 × 4, then 200 mg QD	4816.00
Itraconazole PO capsule	200 mg QD	390.60
Itraconazole PO capsule	400 mg QD	781.20
Itraconazole PO solution	200 mg QD	396.00
Itraconazole PO solution	400 mg QD	792.00
Liposomal amphotericin B	3 mg/kg (70 kg) QD	8498.40
Liposomal amphotericin B	4 mg/kg (70 kg) QD	12,747.60
Liposomal amphotericin B	5 mg/kg (70 kg) QD	14,872.20
Amphotericin B	1 mg/kg (70 kg) QD	169.20
Candidiasis		
Caspofungin IV	70 mg × 1, then 50 mg QD	8265.65
Fluconazole IV	400 mg × 1, then 200 mg QD	2322.39
Fluconazole IV	400 mg QD	3342.90
Fluconazole PO	400 mg × 1, then 200 mg QD	327.36
Fluconazole PO	400 mg QD	633.60
Voriconazole PO	400 mg q12	2930.40
Empiric therapy		
Amphotericin B	1 mg/kg (70 kg) QD	169.20
Liposomal amphotericin B	3 mg/kg (70 kg) QD	8498.40
Voriconazole IV	6 mg/kg q12 × 2, then 3 mg/kg q12 (70 kg)	5147.86

*Adapted from references 24 and 29.

IV indicates intravenous; PO, oral; QD, every day; q12, every 12 hours.

itraconazole capsules, voriconazole does not require acid for dissolution in the gastrointestinal tract and may be administered with antacids and other acid-suppressing agents. (Of note, itraconazole solution is available and does not require acid for dissolution, but it is not palatable and patient compliance may be of concern.) Voriconazole may cause visual disturbances, although the disturbances tend to diminish after continued therapy. Vision does not appear to be affected in the long term, although only treatment periods up to 28 days have been studied. Voriconazole may also cause hepatic toxicity, although this has been reported with other triazole drugs as well. Renal toxicity has been reported with voriconazole, but patients were on other nephrotoxic agents concomitantly. Dermatologic reactions have also been reported with voriconazole. Drug interactions are common with voriconazole, although the other triazole agents also have significant interaction profiles. Resistance to voriconazole has not been thoroughly studied. However, fungal isolates resistant to fluconazole or itraconazole have decreased susceptibility to voriconazole, suggesting possible cross-resistance.

On the basis of efficacy data, voriconazole is likely as effective as amphotericin B for the treatment of aspergillosis and may be more effective. Voriconazole appears to be effective against infections caused by *Candida* spp., *S. apiospermum*, and *Fusarium* spp. It may be effective for empiric treatment in patients with febrile neutropenia, although more studies need to be conducted to confirm this finding. Use of voriconazole entails lower expenditures than agents such as L-AMB and caspofungin, particularly if patients are switched to oral therapy within a reasonable time frame.

1. McNeil MM, Nash SL, Hajjeh RA, Phelan MA, Conn LA, Plikaytis BD, Warnock DW. Trends in mortality due to invasive mycotic diseases in the United States, 1980–1997. *Clin Infect Dis* 2001;33:641–647.
2. Florea NR, Kuti JL, Quintiliani R. Voriconazole: a novel azole antifungal. *Formulary* 2002;37:389–399.
3. Denning DW. *Aspergillus* species. In Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 5th ed. Orlando: Churchill Livingstone, 2000:2681–2682.
4. De Pauw BE. New antifungal agents and preparations. *Int J Antimicrob Agents* 2000;16:147–150.
5. VFEND (voriconazole) tablets and injection [package insert]. New York: Pfizer, Inc, 2002.
6. Hoffman HL, Rathbun RC. Review of the safety and efficacy of voriconazole. *Expert Opin Investig Drugs* 2002;11:409–429.
7. Terrell CL. Antifungal agents. Part II. The azoles. *Mayo Clin Proc* 1999;74:78–100.
8. Pfizer Global Research and Development. Background document for the Antiviral Drug Products Advisory Committee meeting October 4, 2001: voriconazole tablets and voriconazole injection. Available at http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2_02_FDA-voriconazole.pdf; accessed September 20, 2002.
9. Lazarus HM, Blumer JL, Yanovich S, Schlamm H, Romero A. Safety and pharmacokinetics of oral voriconazole in patients at risk of fungal infection: a dose escalation study. *J Clin Pharmacol* 2002;42:395–402.
10. Schwartz S, Milatovic D, Thiel E. Successful treatment of cerebral aspergillosis with a novel triazole (voriconazole) in a patient with acute leukaemia. *Br J Haematol* 1997;97:663–665.
11. Goldstein JA. Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. *Br J Clin Pharmacol* 2001;52:349–355.
12. Johnson EM, Szekely A, Warnock DW. In-vitro activity of voriconazole, itraconazole and amphotericin B against filamentous fungi. *J Antimicrob Chemother* 1998;42:741–745.
13. Abraham OC, Manavathu EK, Cutright JL, Chandrasekar PH. In vitro susceptibilities of *Aspergillus* species to voriconazole, itraconazole, and amphotericin B. *Diagn Microbiol Infect Dis* 1999;33:7–11.
14. Manavathu EK, Cutright JL, Chandrasekar PH. Organism-dependent fungicidal activities of azoles. *Antimicrob Agents Chemother* 1998;42:3018–3021.
15. Lass-Florl C, Nagl M, Speth C, Ulmer H, Dierich MP, Wurzner R. Studies of in vitro activities of voriconazole and itraconazole against *Aspergillus* hyphae using viability staining. *Antimicrob Agents Chemother* 2001;45:124–128.
16. Ruhnke M, Schmidt-Westhausen A, Trautmann M. In vitro activities of voriconazole (UK-109,496) against fluconazole-susceptible and -resistant *Candida albicans* isolates from oral cavities of patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997;41:575–577.
17. Pfaller MA, Diekema DJ, Jones RN, Sader HS, Fluit AC, Hollis RJ, Messer SA. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through

1999 in the SENTRY antimicrobial surveillance program. *J Clin Microbiol* 2001;39:3254–3259.
18. Pfaller MA, Messer SA, Hollis RJ, Jones RN, Diekema DJ. In vitro activities of ravuconazole and voriconazole compared with those of four approved systemic antifungal agents against 6,970 clinical isolates of *Candida* spp. *Antimicrob Agents Chemother* 2002;46:1723–1727.
19. Meletiadis J, Meis JF, Mouton JW, Rodriquez-Tudela JL, Donnelly JP, Verweij PE. In vitro activities of new and conventional antifungal agents against clinical *Scedosporium* isolates. *Antimicrob Agents Chemother* 2002;46:62–68.
20. Espinel-Ingroff A. In vitro fungicidal activities of voriconazole, itraconazole, and amphotericin B against opportunistic moniliaceous and dematiaceous fungi. *J Clin Microbiol* 2001;39:954–958.
21. Nesky MA, McDougal EC, Peacock Jr JE. *Pseudallescheria boydii* brain abscess successfully treated with voriconazole and surgical drainage: case report and literature review of central nervous system pseudallescheriasis. *Clin Infect Dis* 2000;31:673–677.
22. Denning DW, Ribaud P, Milpied N, Caillot D, Herbrecht R, Thiel E, Haas A, Ruhnke M, Lode H. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis* 2002;34:563–571.
23. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, Sylvester R, Rubin RH, Wingard JR, Stark P, Durand C, Caillot D, Thiel E, Chandrasekar PH, Hodges MR, Schlamm HT, Troke PF, de Pauw B. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;347:408–415.
24. Walsh TJ, Pappas P, Winston DJ, Lazarus HM, Petersen F, Raffalli J, Yanovich S, Stiff P, Greenberg R, Donowitz G, Schuster M, Reboli A, Wingard J, Arndt C, Reinhardt J, Hadley S, Finberg R, Laverdiere M, Perfect J, Garber G, Fioritoni G, Anaissie E, Lee J. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002;346:225–234.
25. Powers JH, Dixon CA, Goldberger MJ. Voriconazole versus liposomal amphotericin B in patients with neutropenia and persistent fever. *N Engl J Med* 2002;346:289–290.
26. Apisarnthanarak A, Little JR, Tebas P. Voriconazole versus liposomal amphotericin B for empirical antifungal therapy [correspondence]. *N Engl J Med* 2002;346:1745–1747.
27. Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz C, Bodensteiner D, Pappas P, Seibel N, Greenberg RN, Dummer S, Schuster M, Holcenberg JS. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med* 1999;340:764–771.
28. Prentice HG, Hann IM, Herbrecht R, Aoun M, Kvaloy S, Catovsky D, Pinkerton CR, Schey SA, Jacobs F, Oakhill A, Stevens RF, Darbyshire PJ, Gibson BE. A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Haematol* 1997;98:711–718.
29. Ally R, Schurmann D, Kreisel W, Carosi G, Aguirrebengoa K, Dupont B, Hodges M, Troke P, Romero AJ. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. *Clin Infect Dis* 2001;33:1447–1454.
30. Tan KKC, Brayshaw N, Oakes M. Investigation of the relationship between plasma voriconazole concentrations and liver function test abnormalities in therapeutic trials. Presented at 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill, December 2001: abstract A-18.